Novel Interventions for Treating PTSD: Preliminary Studies

Alina Suris, Ph.D., ABPP

Chief of Psychology, Mental Health
VA North Texas Health Care System
Associate Professor of Psychiatry
UT Southwestern Medical Center
Translational Studies

• Memory at the Cellular Level:
  ✓ Augmentation of extinction
  ✓ Interference with fear memory reconsolidation
Extinction of Trauma Memories

- People with PTSD associate certain cues with danger. (e.g. IED in the road)
- Extinction has not occurred naturally in a person with PTSD, but it can be learned.
- Extinction modifies the fear response. It involves learning that a once fear-inducing stimulus is no longer dangerous.
- Extinction does not erase any memories; it involves new learning that old, threatening cues are now safe.

- Classical fear conditioning paradigm in which novel environment is paired with a footshock.
- 48 hours later re-expose mice to environment = sig. fear response (reactivation of fear memory)
- 2-5 minutes later injected with various doses of glucocorticoid, anisomycin, or vehicle.
- 24 hours later mice re-exposed to environment

Results

- When glucocorticoids are administered to male C57BL/6 mice immediately after reactivation of a contextual fear memory, subsequent recall is significantly diminished (3 and 10 mg/kg)
- Glucocorticoids decrease fear memory retrieval and augment fear memory extinction
Hypotheses

Single dose of hydrocortisone paired with therapeutic traumatic memory reactivation will augment traumatic memory extinction as measured by:

• PTSD symptom reduction (IES-R score)
• Physiological responses to own trauma memory
## Translational Study Procedures

<table>
<thead>
<tr>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Cortisol Rx</strong></td>
<td><strong>Exposure</strong></td>
<td><strong>Follow-up</strong></td>
</tr>
<tr>
<td>Measurements:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life events</td>
<td>UDS</td>
<td>UDS</td>
<td>CAPS (worst)</td>
</tr>
<tr>
<td>CAPS</td>
<td>IV inserted</td>
<td>IMAGERY</td>
<td>IES-R (both events)</td>
</tr>
<tr>
<td>SCID</td>
<td>Worst trauma</td>
<td>(neutral, trauma) x2</td>
<td></td>
</tr>
<tr>
<td>IES-R</td>
<td>- describe</td>
<td>- physio testing</td>
<td></td>
</tr>
<tr>
<td>QIDS</td>
<td>- IES-R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>- Q&amp;A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2\textsuperscript{nd} worst trauma:
- describe
- IES
- Q&A

**Rx CORTISOL**
(4mg/kg)
QIDS

IES-R
QIDS
Script Preparation

• 30-45 seconds in duration portraying each experience in the second person, present tense

• Uses 5 of the selected bodily responses (or as many as the patient selected, whichever is less)

• The standard script describes neutral experiences (2) used in several previously published studies.

• Scripts are recorded and saved as .wav files that will then be replayed to the subjects to reactivate their traumatic memories
It's 1990 and you're in Iraq. Your squad is mine sweeping, doing everything by the book. Your friend that you have known all your life is on point. Your heart pounds and your palms are clammy. He goes into the field and takes 3 steps. Your stomach is in knots. You hear an explosion. Your body feels heavy as you clench your fist. Over half of your friend's body is gone. Your hands are trembling and your eyes are closed. You were his squad leader and now he’s gone. You want to scream.
Neutral Scene

You are sitting in a lawn chair on your porch on a summer afternoon. Leaning back, relaxed, you feel a soft warm breeze blowing across the porch. A green lawn stretches out before you, and scattered trees sway gently with the wind. Comfortable and content, you are so relaxed you hardly move while you sit in the chair enjoying the pleasant summer day.
Mean PTSD Score by Symptom Group for Worst Trauma

Posttraumatic Symptom Score Means

- Intrusion (B)
  - Cortisol: 2.7
  - Control: 3.0

- Avoidance/ Numbing (C)
  - Cortisol: 1.9
  - Control: 2.7

- Arousal (D)
  - Cortisol: 2.6
  - Control: 3.0

*p = .019

* indicates significant difference between groups.
Conclusions

- Pairing of traumatic memory activation with a single dose of glucocorticoid resulted in lower Group C (avoidance/numbing) scores in the hydrocortisone group one week after treatment.

- Group C symptoms are marker of psychopathology in PTSD and reduction of problematic avoidance behaviors a major therapeutic endpoint of exposure therapies.

- Effects were not observed one month later suggesting that the observed effects of a single glucocorticoid dose may be transient.

- It is possible that multiple pairings of memory activation with cortisol might further enhance the effects and extend them across all PTSD symptom domains.

Double Blind Randomized Placebo Controlled Trail

- Participants who receive an exogenous glucocorticoid (Cort) 60 minutes prior to traumatic memory reactivation will have fewer PTSD and depression symptoms one week later.

- Reduction effects will be cumulative (4 doses of drug).

- Decreases in PTSD and depression symptoms will persist at 1, 3, and 6 months.

- Subjects who receive Cort will demonstrate decreased physiological responses one week later and it will persist at follow-ups.

  dose = .15mg/kg (approx 10 mg for 70kilo man)
Interference with Reconsolidation of Trauma Memories

New traumatic memories are initially labile and sensitive to disruption before being consolidated into long term memory. (Dudai, 2004).

When reactivated, they become newly labile and must be reconsolidated to remain in long-term memory. (Lupien & Maheu, 2007).

Both consolidation and reconsolidation are sensitive to disruption with pharmological agents, such as protein synthesis inhibitors (e.g rapamycin). (Nader et al., 2000)

Disrupting reconsolidation changes the molecular organization of the memory trace and diminishes the emotional valence of the fearful memory. (Blundell, Kouser, & Powell, 2008; Duvarci & Nader, 2004; Nader et al., 2000; Monfils et al., 2009).

• Administered rapamycin to mice at various times relative to contextual fear conditioning training or fear memory retrieval.

• Mice receiving rapamycin were compared to mice injected with placebo or anisomycin.

Results:

• Rapamycin blocked traumatic memory consolidation.

• Rapamycin inhibited traumatic memory reconsolidation.

Conclusion:

“Systemic rapamycin, in conjunction with therapeutic traumatic memory reactivation, can decrease the emotional strength of an established traumatic memory.”
Proof of Concept

- Single dose of an mTOR kinase (Rap) paired with therapeutic traumatic memory reactivation will selectively inhibit traumatic memory reconsolidation
  - Measured by:
    - Physiological responses to own trauma memory
    - PTSD symptom reduction via self-report and clinician assessed
- Traumatic memory inhibition will be maintained at 1 and 3 months post-administration
Rapamycin-Sirolimus

- Macro cyclic antibiotic produced by a strain of the soil bacterium *Streptomyces hygroscopicus*.
- FDA-approved immunosuppressant.
- Inhibits mTOR activity needed for protein synthesis during memory consolidation and reconsolidation.
Study Procedures--Detail

**Visit 1**
Baseline

Consent
Measures:
- TBI Measure (R-BANS A)
- CAPS
- PCL
- QIDS
Randomization

**Visit 2**
Rapamycin Rx

UDS
Worst trauma
  - describe
  - Q&A

20 minutes
  - PCL
  - QIDS

Rx Rapamycin

**Visit 3**
Exposure

UDS
IMAGERY
  neutral, trauma
  - physio testing

PCL
QIDS

**Visit 4 & 5**
Follow-up (1 & 3 months)

TBI Measure (R-BANS B)
- CAPS
- PCL
- QIDS
Results N=51

• No significant differences between groups on PTSD measures or physiology measures

• Clinically meaningful improvement was observed in 40% of the sirolimus group vs. 16% of the control group one month post-treatment.

• At three months post-treatment, 44% of the sirolimus group had clinically significant improvement vs 29% of the control group.
Further Analyses

• To explore recency effects of combat exposure, we separated the group into Vietnam veterans & OEF/OIF-Desert Storm

• Vietnam veterans did not differ between groups (sirolimus and placebo) on outcome measures

• However---we found differences in the younger cohort
Mean CAPS and PCL scores at one month by treatment group OEF/OIF- Desert Storm subsample, \( n = 34 \)

**CAPS**, \( p = .027 \)

**PCL**, \( p = .032 \)
Mean CAPS score over time by treatment group
OEF/OIF /Desert Storm subsample, (n = 34)
Conclusions

• Established safety and feasibility of using Rapamycin combined with reactivation of a traumatic combat-related memory as a potential treatment for male combat veterans with PTSD.

• More recent trauma memories of younger veteran cohorts (i.e., OEF/OIF) appear more amenable to modification

• Future: repeated pairings (e.g., 2-4) of sirolimus and trauma reactivation might be more effective

Why do novel interventions matter?

• Current evidence-based treatments (e.g. Prolonged Exposure, Cognitive Processing Therapy):
  – Require training and supervision of therapists
  – Difficulty recruiting
  – Have large drop-out rates
  – Time intensive (12 to 16 sessions)
  – Emotionally intensive (therapist & client)
  – Research shows some may need more treatment (CPT for Veterans with military sexual trauma)
Frankie and his rat, Elvis